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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,336	03/23/2004	Jacques Jolivet	PHARMA-357	2203

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EXAMINER	
DELACROIX MUIRHEI, CYBILLE	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 04/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/806,336	JOLIVET ET AL.	
	Examiner	Art Unit	
	Cybille Delacroix-Muirheid	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/06/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The following is responsive to the preliminary amendment received Aug. 9, 2004.

Claims 1-47 are presented for prosecution on the merits.

Information Disclosure Statement(s)

Applicant's information disclosure statement received Oct. 6, 2004 has been considered. Please refer to Applicant's copy of the 1449 submitted herewith.

Claim Objection(s)

1. Claims 37, 43-46 are objected to because of the following informalities: in claim 37, line 2, after "further", the term "comprising" should be cancelled and replaced with –comprises--. Additionally, at line 4, before "nucleoside", the term "comprising" should be deleted and replaced with –consisting of--. Please refer to MPEP 2173.05(h) for guidance on proper Markush language.

In claims 43-46, before "troxacitabine", the term "of" should be cancelled. Appropriate correction is required.

2. Claims 9-12 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 9-12 recite a range which is ultimately broader than the range claimed in claim 8. Claim 8 sets a lower limit of 0.03 micromolar, whereas the lower limit of claims 9-12 can be as low as 0.00 micromolar.

Claim Rejection(s)—35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 8-15, 23-28, 33-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pancreatic cancer, large bowel cancer and gastric cancer, does not reasonably provide enablement for treatment of all types and forms of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The claims are drawn to a method for treating a cancer patient, which comprises administering, for at least 72 hours by continuous infusion, an effective amount of troxacitabine to the patient.

(2) The state of the prior art

With respect to cancer, this a broad term which encompasses numerous forms of neoplastic diseases, each involving different types of tissues and organs and also includes blood borne diseases. As recognized in the art, many different anti-neoplastic drugs are used to treat a variety of cancers, but there is no one drug which is capable of treating all cancers in general. Please see pages 1226-1229 of Goodman & Gilman's.

Additionally, Chu et al., recognizes inhibitory activity of troxatyl against a limited number of cancers such as lung, ovarian, renal, prostate, breast, colon, leukemia, melanoma and CNS cancer. Please see col. 14, Table 2.

(3) The relative skill of those in the art

The relative skill of those in the art is high. However, given the state of the art as set forth above, the artisan is currently unaware of any one particular anticancer agent that is effective against all cancer cell types

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical and cancer art is high. Additionally, the lack of significant guidance from the present specification or prior art with regard to the actual treatment of all cancer cell types in a mammal, including a human, with the claimed compound as the active ingredient makes practicing the claimed method unpredictable.

(5) The breadth of the claims

The complex nature of the subject matter to which the present claim is directed is exacerbated by the breadth of the claim. The claim is broad and encompasses treatment of a vast number of possible cancer types including solid tumors as well as blood-borne tumors.

(6) The amount of direction or guidance presented

Applicant's specification appears to only be enabled for the treatment of solid tumors, colorectal tumors and leukemia. It does not enable one of ordinary skill in the art to use the claimed invention in the treatment of the numerous neoplastic diseases covered by the term "cancer." Applicant's specification does not set forth a representative number of examples of cancers, which would be treated by the claimed compound.

(7) The presence or absence of working examples

The only working examples in the specification involve clinical studies involving the use of patients suffering from solid tumors as well as patients suffering from relapsed acute myelogenous leukemia. The specification also discloses the results from human xenograft studies involving colorectal cancer cell lines. Please see pages 16-26.

(8) The quantity of experimentation necessary

Since the prior art recognizes that no one compound is capable of treating the vast number of possible cancerous diseases encompassed by the term "cancer"; (2) the prior art recognizes activity of the claimed compound against a limited number of cancer types (Chu et al.); (3) the specification shows anti-tumor activity only against leukemia,

solid tumors and colorectal cancer and (4) since the claims are very broad and include treatment of any type of cancer ranging from solid cancers to blood borne cancers, one of ordinary skill in the art would be burdened with undue experimentation to determine which cancers would be treated by administration of the claimed compound.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 38, 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41 recites the limitation "wherein said at least one further therapeutic agent is a cytokine" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim 38 contains the trademark/trade name "Gleevec®". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe the compound imatinib mesylate and, accordingly, the identification/description is indefinite.

The Examiner respectfully suggests that applicant amend the claim to include the name of compound.

Claim Rejection(s)—35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claim 47 is rejected under 35 U.S.C. 102(a) as being anticipated by Leblond et al. (abstract #2633).

Leblond et al. disclose a method of treating mice suffering from colon tumors, the method comprising administering, by continuous infusion for 6 days, an effective amount of troxacitabine to the mice. Leblond et al. teach that anti-tumor efficacy was related to doses and the duration of administration. Please see the abstract.

Claim Rejection(s)—35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gourdeau et al., 6,747,036 in view of Chu et al., 5,817,667 and LeBlond et al. (#2633).

Gourdeau et al. disclose a method of treating leukemia (AML, CML, etc.) in a patient in need thereof by administering to the patient an effective amount of a compound represented by Formula (I), more specifically, the compound (β-L-oddC), i.e. troxacitabine or a salt thereof. Troxacitabine is administered (intravenously) to the patient by continuous infusion at a dosage of 0.01 to about 5.0 mg/kg/hour. Gourdeau et al. teach that troxacitabine is administered to achieve peak plasma concentrations of the compound of from about 1 to about 751 μM, preferably about 2 to 50 μM, more preferably about 3 to 30 μM.

Gourdeau et al. additionally disclose a method of treating leukemia in a patient by administering an effective amount of troxacitabine in combination with other

chemotherapeutic agents such as bleomycin or cyclophosphamide, etoposide, PSC 833, monoclonal antibodies and cytokines, interferons, interleukins, colony stimulating factors, rituxan, IL-2, IL-3, etc. Furthermore, the active agents involved in the combination therapy may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Please see col. 2, line 53 to col. 3, line 67; col. 5, lines 5-15 and lines 55-67; col. 6, line 18 and lines 47-50; col. 7, line 63 to col. 8, line 40.

Gourdeau et al. do not disclose a method of treating other types of cancers such as pancreatic cancer, prostate cancer, breast cancer, ovarian cancer etc. Yet, the Examiner refers to Chu et al., which teach a method of treating cancers such as a pancreatic cancer, leukemia, prostate cancer breast cancer, ovarian cancer etc., the method comprising administering (intravenously) an effective amount of (-)-OddC, i.e. troxacitabine, or a salt thereof to a patient in need thereof. Chu et al. additionally disclose that (-)-OddC can also be administered in combination with other known anticancer agents. Please see col. 3, lines 10-52; col. 10, lines 54-61.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Gourdeau et al. to additionally treat other cancers such as pancreatic cancer because Chu et al., disclose that troxacitabine exhibits anti-tumor activity and one of ordinary skill in the art would reasonably expect troxacitabine to demonstrate anti-tumor activity not only against leukemia but also against other tumors such as pancreatic tumors. Moreover, Chu et al.

clearly teach and thus suggest troxacitabine's use in the treatment of cancers other than leukemia.

Additionally, Gourdeau and Chu do not disclose continuous infusion of troxacitabine for at least 72 hours; however, the Examiner refers to Leblond et al., which disclose a method of treating mice suffering from colon tumors, the method comprising administering, by continuous infusion for 6 days, an effective amount of troxacitabine to the mice. Leblond et al. teach that anti-tumor efficacy was related to doses and the duration of administration. Please see the abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the methods of Gourdeau and Chu to administer troxacitabine for at least 72 hours (or 6 days) because, in view of the desirable results obtained by Leblond et al., one of ordinary skill in the art would reasonably expect anti-tumor efficacy when troxacitabine is administered continuously for at least 72 hours.

Additionally, since Leblond et al. establish that dosage and duration of administration are necessary for anti-tumor efficacy, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the methods of Gourdeau and Chu such that troxacitabine is administered at a dose and for a period of time to establish therapeutic blood plasma concentrations effective to result in anti-tumor activity sufficient to treat the patient suffering from cancer.

Conclusion

Claims 1-47 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Cybille Delacroix-Muirheid** whose telephone number is **571-272-0572**. The examiner can normally be reached on Mon-Thurs. from 8:30 to 6:00 as well as every other Friday from 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Christopher Low**, can be reached on **571-272-0951**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CDM
April 3, 2005

Cybille Delacroix-Muirheid
Patent Examiner Group 1600